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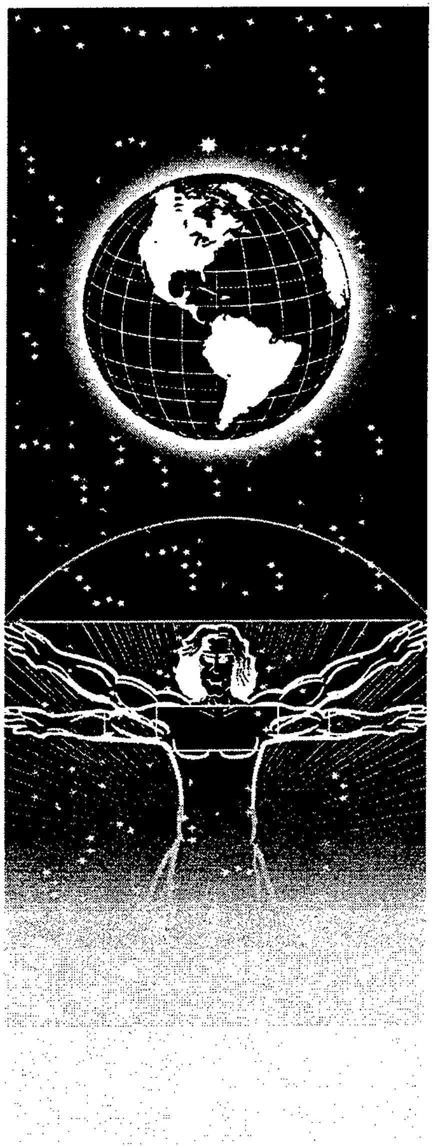

UNITED STATES AIR FORCE RESEARCH LABORATORY

SUBTLE MEASUREMENT OF BEHAVIOR EFFECTS OF MICROWAVE RADIATION

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This report has been reviewed and is approved for publication.

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13. ABSTRACT *(Maximum 200 words)*
The primary objective of this task was the development and application of experimental procedures to characterize the behavioral effects of exposure to radio frequency radiation (RFR) fields. Two mechanisms were considered. First, the effects may be part of normal behavioral thermoregulation, an adaptive response; or they may represent a non-adaptive injurious process. That RFR produces injury following an exposure of sufficient intensity and duration is well known. The mechanism or mechanisms which act at lower or shorter exposures have not been characterized. Behavioral effects of RFR exposure which are part of normal thermoregulation, may be analyzed as any other physiological event for which the organism has system of responses. That is, RFR may act as a discriminative stimulus, guiding changes in performance; and it may act as a reinforcer, motivating behavioral change. The approach taken was to investigate the extent to which these two behavioral functions, discrimination and reinforcement, could be applied to RFR bioeffects. In the first experiment, rats were trained to detect 9.3 GHz RFR. Thresholds were at or below those previously reported for human detection at this frequency. In the second experiment, methods were developed to scale the motivation produced as a reinforcer, in this case RFR exposure both in isolation and in the presence of a second reinforcer. Unfortunately, in spite of success at establishing discrimination based on 9.3 GHz as a stimulus, attempts to establish escape and avoidance of brief bursts of 9.3 GHz failed. Following repeated exposures to short bursts (0.5 to 5 sec) of high power RFR, the rats previously trained to avoid shock failed to bar press to avoid RFR. Rather, their response was to assume a prone position, a response characteristic of hyperthermia in rats. The failure may have been the result of the relatively low power output (800 W) of the transmitter. It was concluded that short high-power bursts of RFR may effectively motivate behavior only at higher frequencies (e.g., 9.3 GHz or greater) and/or higher power than could be applied in the present study.

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PREFACE

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The care and use of animals in this study was in compliance with Department of the Air Force Regulation 169-2. All animal resource programs and facilities are fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC). The Air Force Research Laboratory complies with the National Institute of Health on Humane Care and Use of Animals, the Animal Welfare Act and all other applicable federal, state and local laws.

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Introduction

The growing application of microwave (RF) technology has increased the potential for hazardous human exposures. The potential hazard posed by this expanding use of RF technology requires an ongoing study of RF bioeffects to keep pace with new applications and technologies. Furthermore, exposures to new and future sources are likely to involve RF power levels and exposure parameters (e.g., frequency, pulse width, peak power, etc.) which have yet to be studied. Effects on performance are among the most sensitive indices of biological effects (Elder and Cahill, 1984) and is a necessary part any research program to characterize RF hazards. In addition, many safety issues require understanding potential performance effects. For example, interference with self-rescue or task performance by RF exposure represent two performance mediated hazards.

Most experiments attempting to measure the behavioral effects of RF fields proceed by first training a pattern of behavior which was typically motivated by food. Once the performance was stable, the organism was exposed to an RF field and its performance on the trained task tested either during or more typically after the exposure. Effects reported by such experiments are typically assumed be a result of the thermal challenge posed by the RF exposure.

The thermoregulatory behaviors induced by a RF exposure are likely to be the first visible effect of the exposure seen by an observer. They represent a motivational effect of RF exposure. Investigators have reported observing thermoregulatory behaviors in animals trained on non-thermoregulatory baselines, but these observations have not been done systematically (Sanza and de Lorge, 1977; D'Andrea et. al., 1979; and Lebovitz,1981). Organisms trained on thermoregulatory baselines have appropriately altered their performance during RF exposure (Adair, 1979; Adair and Adams, 1980; and Stern et al, 1979). Stern et. al. (1979) were able to maintain behavior with RF reinforcer in a cold environment. However, difficulties have been noted by researchers attempting to maintain escape and avoidance responses in a thermally "neutral" environment (Carroll, et al., 1980; Levinson, et al., 1981, 1982). Levinson, et al found that rats would learn to occupy a "safe area" to extinguish a 918 MHz field with a whole-body-averaged dose rate of 60 mW/g, only if the presence of the field was signalled by a light. No such signalling was required for rapid acquisition of the same response when foot shock was substituted for the RF (Carrol, et al., 1980).

One possible explanation for the apparent ineffectiveness of RF in previous experiments was the long detection latencies on the order of tens of seconds for part-body warming (up to 75 mW/cm^2) and the long persistence of the warming following termination of the RF reported by Hendler, et al. (1963) and Schwan, et al. (1966). The gradual onset and offset of warming from RF may be difficult to detect, and difficult to associate with an effective escape response which would terminate the RF immediately but not the sensation of heat.

The purpose of the present experiment was to determine the threshold detection in brief (less than 10 sec) exposures to a 9.3 GHz RF field. During any given session the rats were required to report the presence of any of three different RF intensities or no RF.

Method

Subjects

Twelve male Sprague Dawley rats three months old were individually housed and allowed to adapt to the vivarium for 10 days. All rats were maintained at approximately 350 grams throughout the experiment. The reasons for this weight control regimen were dual: First, drastic changes in the size of a rat alter the

distribution of RF energy. Second, research has shown (McCay et al, 1935; Weindruch et al, 1979; and Geokas et al, 1990) that the life expectancy and health of rats is improved by restricting access to food. If a rat's weight declined below 315 grams (a 10% decrease) supplementary food was provided at the end of that day. Persistent weight loss was addressed by lowering the ratio for that rat within the experiment until it maintained at least a 350 grams. Weekend feedings were adjusted such that Monday AM weights will approximate Friday AM weights.

Apparatus

Training chambers. Initial training was conducted in 8 modular rat chambers (Coulbourn Instruments, Allentown, Pa.). All stimuli and response levers were standard modules. The intelligence panel of these chambers are configured by placing modules and or blank spacers in three vertical tracks. The center track had a combination feeder/dipper module that delivered the 45 mg food pellet reward (BioServ, Frenchtown, NJ). The food-cup opening was 4.5 cm wide by 6.0 cm high with the bottom edge 5.5 cm from the floor. On either side (10.0 cm from the floor) and above the feeder opening (18.5 cm from the floor) was a response lever. Three cue lamps were located 4.0 cm above each of the three response levers. A house light was located along the top of the intelligence panel (32 cm from the floor) directly over the feeder, to the left of the house light was a sonalert (32 cm from the floor) and to the right a speaker (32.5 cm from the floor). A feedback relay module was located directly under the house light behind a blank panel.

Exposure Chamber. The test chamber had the same physical dimensions as the training chambers, except that all components constructed of Lexan to minimize interaction with the RF field. All electrical components except the pellet dispenser were located outside of the anechoic chamber. Cue lights were presented by means of fiber-optic cables focused on colored, plastic lenses. The house light was composed of six fiber-optic cables attached in a circle 2 cm in diameter to the top of the chamber centered with respect to the intelligence panel and 4 cm from the top edge of the panel. Bar presses interrupted a fiber optic circuit between an infrared emitter and detector (Coulbourn Instruments, Allentown, Pa.) located outside the exposure chamber. Food pellets were dispensed by a standard pellet dispenser raised 80 cm above the chamber and out of the RF field. Pellets traveled down a Tygon tube to the food cup. A feedback relay sounded with each appropriate depression of a lever.The feedback relay was located outside the exposure chamber. The sound traveled down a 10 m long, 6 cm diameter plastic tube to the top left position of the intelligence panel. A Sonalert located with the speaker sounded through the same tube during each pellet delivery. Air was blown into the chamber through a second similar tube by a fan located outside the anechoic chamber.

RF Field. Exposures were conducted using the peak power emission simulator (COBER) X-band 9.3 GHz emitting pulses 1-microsecond wide at a maximum rate of 1 Khz, a 0.1 percent duty-cycle. This was set to produce at a maximum average forward power of 200 W, a 20,000 KW peak power, and 57.8 mW/cm^2 at the food cup, when pulsed at 1 KHz. Far field started 75 cm from the horn. Repetition rate was decreased from the maximum 1.0 kHz (200 W average forward power) to produce lower power densities. Specific absorption rate (SAR) determined by single-dwell calorimetry was 44 mW/g/kW of average forward power.

The horn was in ZEH orientation pointing horizontally, its bore site 100 cm from the floor of the anechoic chamber. The exposure chamber was orientated such the that the K vector was parallel to the intelligence panel. And passed through the chamber 3 cm above the floor and 3 cm in front of the intelligence panel. This approximated the height of a rat's head in front of the food cup. The center lever of the exposure chamber was located 87 cm from the horn. The inside of the right wall was 74.5 cm from the horn and the left wall was 99.5 cm from the horn.

Experimental Control System. A SKED-11 programming system (Snapper, Kadden, & Inglis, 1982) controlled a Micro PDP 11/73 computer (Digital Equipment Corporation, Maynard, Massachusetts) that

controlled specified experimental events including the operation of the transmitter, and recorded data with a resolution of 10 ms.

Procedure

Session durations were adjusted from an initial value of 60 minutes to maintain each rats body weight. Sessions were conducted on Mondays through Fridays each week. On these days, food was available only in the form of the pellet reinforcer delivered during the behavioral sessions. An additional allocation of standard rat chow was given on Friday afternoons, individually adjusted so that body weights on Monday mornings equaled those of the prior Friday morning, and to insure that Monday performance was comparable to performance on other days.

RF detection was tested in the 3-lever plastic chamber located in a RF anechoic chamber. Rats were trained to detect brief bursts of RF energy using a trials procedure. Trials were initiated by the completion of 4 responses on the center, "observing" lever. The pulses were emitted (RF trials) or not (NO-RF trials) for a minimum of 6 seconds. A final "observing" response enabled the right and left "choice" levers. The first "choice" response was reinforced with a flash of the food cup light and a 45 mg food pellet, if correct (hits and correct rejections), or a time-out, if an error (misses and false alarms). If no response was made within 10 seconds the trial was terminated. Training was started at three power densities: 57.8, 53.9, and 51.1 mW/cm^2 (SAR 8.9, 8.4, and 7.9 mW/g, respectively). These were presented randomly in each session. As performance improved the power densities were gradually decreased each time highest density was detected over 80% of the time (the difference between the probability of a hit and a false alarm was at least 80%) and the lowest power density was detected over 60% of the time.

Results and Discussion

Only data from trials whose sample stimulus was randomly selected were used in the data analysis. The sample stimulus for all other trials was determined by a correction procedure which repeated trials until a correct response occurred. The correction procedure prevents the development of alternate strategies by the subject. However, as it repeats incorrect trials, prior incorrect trials are potential cues other than the sample stimulus. Therefore, only trails following a correct trial were used in the data analysis.

Two response procedures define one choice response, say, a left lever press, as the RF-present response and the other choice response, a right lever press in this example, as a no-RF-present response. Data from such a procedure can be analyzed in terms of signal detection theory (Green and Sweets, 1966). The advantage of this approach is that it allows the separation of any systematic bias on the part of a subject from that subject's ability to detect the sample RF. Signal detection theory (SDT) divides the trials into four categories based on the presence or absence of the sample stimulus, RF in this study, and the occurrence of either a RF-present response or a no-RF-present response. The RF response, was rewarded only when the sample stimulus was RF, called a "hit". Failure to detect the presence of the RF, that is a no-RF responses in the presence of RF is called a "miss". A no-RF response when no RF was present is called a "correct rejection". And an RF response in the absence of an RF stimulus in called a "false alarm".

The probability of each of the four outcomes (hit, miss, correct rejection, and false alarm) is calculated in terms of the presence or absence of the RF sample stimulus (the independent variable). In other words the probability of a hit is equal to the number of hits divided by the number of opportunities to make a hit or the number of hits plus the number of misses (the two trial types presenting a RF sample stimulus). The probability of a miss is the number of misses divided by that same sum. Thus, the probability of a miss is always one minus the probability of a hit. Similarly, the probability of a correct rejection is the number of correct rejections divided by the number of trials where RF was NOT presented or the number of correct rejections plus the number of false alarms. The probability of a false alarm is calculated by dividing the number of false alarms by the same sum as was used for correct rejections. Thus, the probability of a false

alarm is always one minus the probability of a correct rejection. Since the probabilities of hits and misses must always sum to one and the probabilities of correct rejections and false alarms must also sum to one, the performance may be described by using only the probability of a hit and the probability of a false alarm.

In Figure 1 the probabilities for hits and false alarms are plotted for each rat for the last 10 sessions at the lowest three SAR's each rat was able to detect. At higher SAR's, on the right, the difference between the probability of a hit and the probability of a false alarm are the greatest. At lower SAR's the difference decreases. That is, the top line of hits converges with the bottom line of false alarms. Where the two meet is determined by that rat's bias towards one response or the other.

Five rats were successfully trained to detect the RF field. Two rats reliably detected power densities as low as 2.5 mW/cm^2 (SAR 0.4 mW/g), and a third as low as 3.8 mW/cm^2 (SAR 0.6 mW/g). Two others failed to reliably detected levels lower than 20.8 and 26.5 mW/cm^2 (SAR 2.8 and 4.5 mW/g) in spite of extended training. Figure 1 shows the probability of detection and of error at the final RF intensities for each rat. The X axis shows the SAR of the RF stimulus. The Y axis shows the probability of each outcome for a sample. Though 2 rats did not detect levels as low as the other three, all of the rats showed lower probability of hits and higher probability of false alarms as the RF intensity was decreased. Of the two rats showing higher thresholds, one was subject to occasional seizures (Rat 122) during the final months of the experiment. The other high-threshold rat (Rat 125) was repeatedly observed with his head in the food cup whenever he was not pressing the lever, This habitual "goal tending" may explain his reduced sensitivity to the RF.

This experiment demonstrated that brief bursts of low level pulsed 9.3 GHz RF may function as a discriminative stimulus. Three of the 5 rats reliably detected 9.3 GHz power densities lower (and 2 of those three rats by 75% lower) than the old exposure standard of average power density of 10 mW/cm^2. It seems likely that the rats were able to take advantage of higher localized SAR (See section IV on the use of temperature sensitive paint) produced by the presence of the subject in the RF field.

A true threshold would be a stimulus magnitude below which the stimulus is never detected and above which the stimulus is always detected. The usual finding in psychophysical studies is that some stimulus intensities are detected with a probability greater than zero but less than one. Thresholds are then defined as the intensity with some probability of being detected. Threshold as used by Blick et. al. (1995) was defined as that intensity which was detected with a probability of 0.67. Blick et. al. tested human subjects' ability to detect 10 sec exposures to various frequencies and intensities. Only the intensity which was detected 67% of the time was reported. At 9.3 GHz, on average the humans detected 19.5 mW/cm^2 with that level of accuracy. From the figure presented above, the same likelihood of detection occurred at about 1.83 mW/cm^2 (SAR 0.29 mW/g). It seems likely that the rats had both the advantage of extended practice, and of the exposure of a more sensitive area, the head in the present study versus the back in the human experiment.

In a pilot experiment, it was observed that rats which increased the duration of the RF stimulus by delaying the response on the side levers showed improved performance. Other researchers (Laties, 1972) have reported that when delay improves performance, rats have been observed to develop "intermediate" responses which, though not required by the schedule, allow the rat to produce the delay. It is possible that the rats which had higher thresholds failed to develop sufficiently effective delaying responses.

Increased use of RF emitters has heightened the potential for human exposure. Accidental RF exposures, especially to higher powers, may be terminated when the exposed individual detects the RF and escapes. Changes in performance, including detection and escape, are among the most sensitive indices of health effects (Elder and Cahill, 1984). Wherever RF emitters are used, some possibility of human exposure exists. The final safeguard is the exposed human's ability to detect RF. Characterizing this ability is

important to understanding the hazards posed by new and existing RF emitters, for developing safety procedures, educating operators, and in analyzing reports of accidental exposures.

II. PERFORMANCE CONSEQUENCES OF MICROWAVE EXPOSURE: THERMOREGULATION AND TOXICITY

Introduction

Exposure to radiofrequency fields (RF) may impair performance on mission critical task(s). This impairment may result from either powerfully induced thermoregulatory responses, from toxic effects, or both. Thermoregulatory responses include behavioral, biochemical, and physiological processes caused by localized or generalized increases in temperature. Toxic effects include any change which provides no thermoregulatory benefit and may persist even after the RF-imposed thermal challenge has ended. To date, no research designed to distinguish between these two mechanisms has been published. Yet, countering any RF threat requires identifying its mechanism of action. Equipment such as airborne and ground based radar, communication, and electronic warfare facilities are potential sources of exposure. New and future sources of exposure are likely to involve higher powers, and as yet unstudied exposure parameters.

Little is known about the factors which affect RF's capacity to control thermoregulatory behavior or the extent to which these thermoregulatory effects have contributed to previous reports of "nonthermal" toxic effects (Lovely et al, 1983; Stern, 1980; and Justensen, 1979). An experiment which simultaneously measures the effects of RF on thermoregulatory and non-thermoregulatory responses will be able to separate thermal effects from toxic effects. The proposed experiments will measure thermoregulatory and non-thermoregulatory responses and determine the effect on each of a variety of RF exposure conditions.

The first goal of these experiments was to characterize the conditions under which RF motivates thermoregulatory responses. That is, what environmental conditions promote or inhibit RF's effect on thermoregulation? The three environmental parameters likely to alter RF's motivational character were examined: (1) Ambient temperatures above and below the thermal neutral zone, may cause RF to act as a negative or positive reinforcer, respectively. (2) The difficulty or amount of work required may alter RF's capacity as a motivator. And (3) signalling the presence of RF with another stimulus such as a tone or light may also alter RF's capacity to motivate performance.

The second goal of the studies was to characterize RF's capacity to motivate performance relative to a variety of other positive and negative reinforcers. The character of any performance whether it is a human "real-world" performance, or an experimental animal's performance is determined in part by the reinforcing stimulus motivating that performance. For example, a given instance of human behavior, say cooking a steak, may be motivated by a generalized conditioned reinforcer such as money in the case of a professional chef, or by a specific reinforcer such as the steak itself in the case of a person making his or her dinner. Though the form of the two performances may be the same, there are many differences as a consequence of the different motivations. One obvious difference is in the number of steaks prepared under the two motivational conditions. An understanding of the influence different motivations and motivators have on performance is needed, if we are to comprehend the effect on an ongoing performance of introducing the thermoregulatory motivation resulting from RF exposure.

The third goal was to study interactions among these motivators or reinforcers. This would determine exposures which may be tolerated without altering mission performance. Laboratory studies rarely employ more than one reinforcer. However, under most non-laboratory conditions, both humans and animals are subject to the simultaneous actions of multiple reinforcers. Regardless of the mechanism of RF's effects on performance, an assessment of the capacity to perform any another task during or following RF exposure is of critical importance. The final goal was to experimentally separate the motivational effects of RF from any potential toxic effects. Understanding the mechanism(s) of action of RF on performance would suggest methods for minimizing RF's effects. These experiments detected and characterized two kinds of hazard. The first, performance changes produced by attempts to thermoregulate in the presence of a

microwave induced heat load would be motivational effects. And the second, deterioration of all performances including thermoregulation would be a toxic effect. Experiments which fail to make specific provisions to identify the former, motivational effects; may erroneously suggest that a toxic effect is present.

Most experiments attempting to measure the behavioral effects of RF proceed by first training a pattern of behavior typically motivated by food. Once the performance was stable, the organism was exposed to RF and its performance on the task was tested either during or more typically shortly after the exposure. Effects reported by such experiments are typically assumed be a result of the thermal challenge posed by the RF.

Since the induction of thermoregulatory behaviors by a thermal challenge is a normal biological function, RF induced thermoregulation is a motivational effect of RF. When performance is altered and RF does not induce thermoregulation, then this "nonthermal" effect should be considered a toxic effect. The term toxic refers to the failure of normal mechanisms to respond effectively.

A toxic effect, then, includes not only thermal effects which fail to induce any thermoregulatory response, but also any effects which may be truly nonthermal in origin. The description of an RF effect as "nonthermal" implies the unproven assertion that the effect was not result of any thermal change. Since eliminating this possibility is virtually impossible, claims for "nonthermal" effects should be suspect. Rather, the distinction between thermoregulatory versus toxic suggests the testable hypothesis in which appropriate thermoregulation is observed, or inappropriate, nonthermoregulatory changes are observed. To date, no experiments have been able to assign observed performance effects to either thermoregulatory effects or toxic effects. This requires that two performance baselines be simultaneously established in the same organism, one thermoregulatory and one not. Experiments have reported observing thermoregulatory behaviors in animals trained on nonthermoregulatory baselines, but these observations have not been done systematically (Sanza and de Lorge, 1977; D'Andrea et. al., 1979; and Lebovitz,1981). Organisms trained on thermoregulatory baselines have appropriately altered their performance during RF exposure (Adair, 1979; Adair and Adams, 1980; and Stern et al, 1979). But the failure to combine thermoregulatory and nonthermoregulatory baselines makes it impossible to attribute behavioral effects on non-thermoregulatory baselines to either unobserved thermoregulation or a toxic effect. The differentiation of these two potential effects requires a methodology capable of dealing with more than one reinforcement contingency and more than one kind of reinforcer simultaneously.

Microwave Reinforcement: RF of sufficient intensity will pose a thermal challenge which increases the rate of thermoregulatory responses, and necessarily decreasing the rate of other competing responses. Thus, RF may induce thermoregulatory responses that compete against the performance of mission-critical tasks. In this way, RF may alter nonthermoregulatory performance by decreasing the amount of time the organism engages in that task. Numerous experiments have reported RF effects on ongoing or post-exposure operant performance (For a review see Justensen, 1979; Stern, 1980; or D'Andrea, 1991). Similarly, experimenters have been able to modulate ongoing thermoregulatory operant responses maintained by presentation of hot or cold air with relatively low levels of RF (Adair, 1979; and Adair and Adams, 1980). It has also been possible to maintain behavior with RF reinforcer in a cold environment (Stern et al, 1979). Where difficulties have arose in attempting to maintain escape and avoidance responses in a thermally "neutral" environment (Carroll, et al., 1980; Levinson, et al., 1981, 1982). Levinson, et al found that rats would learn to occupy a "safe area" to extinguish a 918 MHz field with a whole-body-averaged dose rate of 60 mW/g, only if the presence of the field was signalled by a light. No such signalling was required for rapid acquisition of the same response when foot shock was substituted for the RF (Carrol, et al., 1980).

One possible explanation for the apparent ineffectiveness of RF in previous experiments is the long detection latencies on the order of tens of seconds for part-body warming (up to 75 mW/cm^2) and the long persistence of the warming following termination of the RF reported by Hendler, et al. (1963) and Schwan, et al. (1966). The gradual onset and offset of warming from RF may be difficult to associate with an effective escape response which would terminate the RF immediately but not the sensation of heat.

A second problem with RF exposure as negative reinforcer is the potentially positive reinforcing effects of the initial warming during RF exposure. Since the preferred ambient temperature of rodents, 28 degrees C, is higher than that of their human experimenters, 24 degrees C; initial exposure to RF in the laboratory is potentially a positive reinforcer. Thus, slow detection and potentially positively reinforcing effects of onset in combination with lack of temporal contiguity of effective escape responses with a decline in temperature may account for failures of rodents to escape from RF. Justensen (1983) reported two experiments in which the typical outcome was death rather than successful escape for naive mice and rats. Rats with a history of intermittent RF exposure, however, did learn to avoid exposure sufficiently to survive. Their performance was unlike that of rats exposed to shock under similar circumstances. Rather than acquiring 100% avoidance as the shocked rats did, the RF rats maintained a intermediate level of avoidance which was related to the intensity of the RF. Justensen concluded that this partial escape suggested thermoregulation rather than simple escape. That is, under the conditions of the experiment, a moderate level of RF exposure was positively reinforcing.

Microwave toxicity: RF may act directly as a toxic agent on the capacity to carry out mission relevant tasks. These toxic effects may be the result of thermal effects which do not occasion any thermoregulatory responses. Numerous experiments, many from the USSR, have reported RF effects which were not attributed to any physiological or behavioral thermoregulatory responses of the organism (See Silverman, 1973; Justesen, 1979; and Stern, 1980). Yet, without explicitly controlling for active thermoregulation, these attributions remain hypotheses.

Concurrent Measurement: No attempts have been made to concurrently measure RF effects on a trained nonthermoregulatory performance and a trained thermoregulatory performance. In such an experiment, any thermal effect of RF would be detected in an increase in the thermoregulatory performance. Any toxic effects of RF could be attributed to deteriorations in both the nonthermoregulatory and the thermoregulatory performances. Such an experiment is necessary if RF effects are to be traced to the intrusion of thermoregulatory responses, or to a toxic effect on ongoing behavior, or both.

Microeconomic Approach: Microeconomics was originally developed to describe the performance of individual human consumers (for an introduction see Samuelson, 1975 and Watson and Holman, 1977). The successful application of microeconomics to the animal behavior both in the wild in studies of foraging and in the laboratory as studies of behavior has provided a rich empirical framework for characterizing numerous reinforcers (Allison et al, 1979; Hursh, 1980; Lea, 1978; Rachlin et al, 1976; and Staddon, 1979). It also suggests that the results of microeconomic studies on animals will generalize easily to humans.

Microeconomic experiments comparing a variety of reinforcers have shown that price can effect a reinforcer's value or demand. For example, heroin injections and electrical brain stimulation (EBS) are two reinforcers thought to be capable of controlling virtually all of a subject's time and effort. And this is true, when the performance requirement or price is minimal. However, if the performance requirement is increased, demand for heroin and EBS decreases rapidly (Hursh, 1980).

In microeconomic terms, the performance requirement is called the price. The demand for a reinforcer is the amount of that reinforcer consumed at a given price. For heroin and EBS, as price increases, demand decreases. Demand which decreases with increases in price is called elastic. Not so for food and water, demand is relatively constant or inelastic as price increases. Inelastic demand, such as that for food or water suggests a necessity. Elastic demand, such as for heroin and EBS suggests a luxury. As prices rise demand for luxuries declines, while the demand for necessities remains the same. Demand measures how an organism regulates its intake of a reinforcer. Therefore, in microeconomic experiments an organism must control its own intake.

The first dimension of demand used by microeconomics to characterize a reinforcer is demand elasticity. Demand elasticity describes the effect of changes in price on changes in demand. Obviously, as the requirements of the price contingency become impossibly high, demand for any reinforcer will approach zero. With more modest price increases, the number of reinforcers earned or demand may decrease, stay the same, or increase. The factors which determine the result characterize the demand elasticity of a reinforcer.

A graphical presentation of demand elasticity is the demand curve. The results of Elsmore (1979) are shown in Figure 1. These demand curves describe effects of price changes on the elastic demand for heroin and inelastic demand for food in two baboons. They also illustrate the inadequacy of the traditional method of comparing reinforcers. The traditional method assumes that the relative reinforcing value of the two reinforcers is constant under conditions of equal price. Clearly, this was not the case. At the lowest price, a 2-minute inter-trial interval, demand for the heroin and the demand for food were approximately equal. As the price of both reinforcers was increased by lengthening the inter-trial intervals, demand for heroin decreased dramatically compared to the relatively constant demand for food. The demand for heroin was much more elastic than the demand for food. This result, produced by differing demand elasticities for food and heroin, cannot be accommodated by the relative value method which requires that the each demand curve be a constant proportion of the other at all prices (Herrnstein, 1961).

The second dimension, opened/closed economy, describes the extent to which alternative sources of reinforcement are available. When there is only a one source of a reinforcer as in the Elsmore experiment, the situation is referred to as a closed economy. In a closed economy for food, an organism must maintain a level of food intake whatever the price, or eventually die. In a closed economy, demand for food is inelastic. Under the same conditions of a closed economy, demand for heroin is elastic.

In an open economy, there are multiple sources of the same or similar reinforcers. Increases in the price at the first source will result in increases in the demand at unchanged alternative sources and a drop in demand at the first source. Demand at the source with the increasing price is elastic. This will hold for reinforcers which in a closed economy show either elastic or inelastic demand. Thus, the presence of alternate sources makes all demand curves more elastic at each source. However, total consumption will retain the character of the single source situation.

In a closed economy, the amount of reinforcement consumed is purely a function of the behavior emitted. There is no minimum and no maximum and no fixed body weight. Open economies are potentially more complicated because the price varies from source to source, and the amount consumed depends upon how behavior is allocated and the various pricing rules. An extreme case, common in many experiments, is produced when the experimenter maintains an animal at a target body weight. In this situation, both a minimum and maximum is guaranteed. The experimenter supplements or limits intake to maintain body weight in a given range. The animal's daily intake is independent of its behavior. In effect, the animal is presented with 2 sources of food. Immediate food from the experimental session and delayed food from the post-session supplements. The typical finding from this method is that as cost in the experimental session increases, demand in the session decreases and is elastic. Laboratory lore has long held that animals forced to earn all of their food within the experimental session show improved performance. That is, more behavior would be emitted. Since this is a closed economy, it creates inelastic demand, and therefore, more behavior at higher prices.

A third microeconomic dimension, substitutable to complementary reinforcers, is also poorly dealt with by the traditional method of comparing reinforcers. This dimension describes changes in demand for a reinforcer as a result of the availability of qualitatively different reinforcers. If a rise in the price of one reinforcer, say potato chips, results in a decrease in potato chip consumption and an increase in demand for a second reinforcer, pretzels. Then pretzels substitute for chips. Conversely, if a decrease in the price of chips increases demand for chips and beer, than the chips and beer are said to be complementary

reinforcers. Complementary demand is applied by many drinking establishments which provide free chips to their customers in hopes of increasing the demand for beer and other beverages. These three basic dimensions of a microeconomic analysis, open and closed economies, elastic versus inelastic demand, and substitutable versus complementary reinforcers, provide a basis for experimentally characterizing and comparing reinforcers, reinforcement contingencies and responses. They provide a means for characterizing the factors such as price, multiple sources, and multiple reinforcers, which influence demand. Previous experiments have addressed the question of the relative value of reinforcers. However, most employed similar methods and suffered from the same problems. Typically, an organism selects among one or more reinforcers. The relative number of responses emitted or time spent making the selections is taken as the measure of reinforcer value (Herrnstein, 1961, 1971, 1979; Herrnstein and Hineline, 1966; Baum, 1973, 1979; see also de Villers , 1977 for a review). This method has several drawbacks.

First, in presenting two or more reinforcers, the experimenter must decide on the size of the unit of each reinforcer to be presented. This decision is critical. If a larger quantity of any given reinforcer has more value, then the outcome may be determined solely by this decision.

Second, the method incorrectly assumes that the delivery of one reinforcer does not alter the value of another reinforcer. This however, is frequently not the case. A common interaction of this type is seen between a dry food reinforcer and a liquid reinforcer. Following the consumption of the dry food reinforcer, the liquid reinforcer is immediately more valued then before. Finally, the method incorrectly assumes that the performance requirement of the reinforcement schedules has no effect on the relative value of the reinforcers presented. In other words, the value of reinforcers is assumed to be the same whether they are easily available or they are difficult to obtain.

These difficulties limit the utility of the traditional method. The application of microeconomic principles to behavior in general has eliminated these limitations. Microeconomics characterizes reinforcing events on several dimensions, rather than the single dimension of relative value analyzed in the traditional method. All of these dimensions interact simultaneously to produce the behavior observed in a given situation (See Hursh (1980) for an introduction.).

<u>Selected reinforcers</u>. Just as the original concern of microeconomists was the human purchase of commodities, behavioral microeconomists have concerned themselves with positive reinforcement. Yet, aversive stimuli are also powerful reinforcers. In these experiments, a microeconomic characterization of four stimuli, food, foot shock, cocaine, and RF were performed (See below for description of each reinforcer.). Extensive information on the microeconomic characteristics of food as a positive reinforcer will provide a basis for comparing the results with the other reinforcers. Shock, a widely used negative reinforcer, will provide a basis for comparing results with other negative reinforcers.

As no microeconomic analysis of any negative reinforcer has been reported, shock is a good first choice. Cocaine has been shown to be a powerful positive reinforcer, but existing data suggest that like heroin demand for cocaine may also be elastic (Bickel et al, 1990).

<u>Performance Requirements: The Schedule of Reinforcement</u>

<u>Intermittent Schedules of Positive Reinforcement.</u> The typical schedule of positive reinforcement consists of two states. In the first state, a house light is illuminated in addition to a cue light associated with a manipulanda, for example a response lever. Upon completion of the schedule requirement, the house light and cue light are extinguished, a reinforcement light is illuminated and the reinforcer is delivered. While the cue light acts as a discriminative stimulus which sets the occasion for a response on the lever.

In the present experiments, the manipulanda is a response lever, the cue light a light just above the lever, and the reinforcement light a cup light. The positive reinforcer and the reinforcement schedule was varied.

Intermittent Schedules of Negative Reinforcement. The experiments proposed here were the first to perform a microeconomic analysis of negative reinforcement. However, previous studies of negative reinforcement schedules have for other reasons varied the price of escape or avoidance of shock. Of these, several maintained performances remarkably similar to that observed with positive reinforcement (e.g. variable interval, Dinsmore, 1962, Perone and Galizio, 1987; fixed ratio, Azrin et al, 1962 and Byrd, 1977; fixed interval, Hineline and Rachlin, 1969; multiple schedule). These negative reinforcement schedules reinforced completion of schedule requirements by terminating a "warning" stimulus for a period of time. In the presence of the "warning" stimulus, an aversive stimulus, say shock, was occasionally presented. Satisfying the schedule requirement avoided shocks which would have been presented and removed or escaped the "warning" stimulus.

Schedule Similarities. The arrangement of stimuli and contingencies for positive reinforcement was analogous to the one for negative reinforcement. In both, the schedule of reinforcement had two states, appropriate responding moved the schedule from the first "work" state to the second "reinforcement" state. Then time moved both schedules from the "reinforcement" state back to the "work" state. In schedules of positive reinforcement, a discriminative stimulus cued responding. In schedules of negative reinforcement, a "warning stimulus" cued responding. Upon completion of the schedule requirement, the second state, a period of reinforcement was cued. In the case of positive reinforcement, the reinforcer was delivered; and in the case of negative reinforcement, a "safety" stimulus was presented and the threat of the aversive stimulus terminated. These similarities undoubtedly account for the similar results which have been reported for positively and negatively reinforced schedules.

Method

In this experiment, demand curves were established employing the two methods, weekly and daily, and different magnitudes of each reinforcer.

Delivery of Positive Reinforcers. Delivery of the positive reinforcers, food, and cocaine will follow each completion of the schedule requirement. The reinforcer was delivered during a brief interval during which the house light and the lights over the response lever in the chamber were extinguished and the lights in the food cup was illuminated. The duration of the reinforcement interval was dependent upon the reinforcer being delivered. Food reinforcement was the delivery of one or more 45 milligram rat chow food pellets. Cocaine reinforcement was the delivery of a small volume of cocaine solution into a small cup.

Delivery of Negative Reinforcers. The negative reinforcement procedure to be employed was selected because it has maintained patterns and rates of behavior similar to that observed on intermittent schedules of positive reinforcement. Furthermore, the appearance of the schedules in terms the sequence of stimuli and events is also the similar. In this procedure, a "warning" stimulus is presented above the response lever and completion of the schedule requirement is reinforced by the removal of the "warning" stimulus and the presentation of the "safety stimulus", the cup light, for a predetermined period of time. A negative reinforcer is delivered at randomly selected intervals during the "warning" stimulus. The "warning" stimulus and the intermittent presentation of the negative reinforcer are ended by the completion of the schedule requirement. Parameters for each negative reinforcer was determined in part by what is found to be effective during training. However, 0.2 milliamperes for 0.25 seconds will represent an initial value for the foot-shock reinforcer. For all aversive stimuli, the bias in selecting of reinforcer magnitudes will always be for lower intensities and shorter durations, unless lower values prove ineffective. Parameters for the tooth pulp stimulation, RF and heat will depend upon the performance of the systems which deliver the stimuli. As a general rule however, the initial intensity was determined by gradually increasing the intensity from zero until a response is clearly observed. Once initial training is complete, lower and higher intensities were explored in quasi-random order to establish similar performance in all subjects of an experimental condition and/or to establish the relationship between intensity and performance depending on the experimental requirements.

Methods for establishing demand curves. Demand curves are determined for any given reinforcer by establishing the quantity of reinforcement purchased at several prices. Price in the context of animal experiments is defined by a schedule of reinforcement. In these experiments, the schedule was a random ratio (RR). All responses in a RR schedule have the same probability of reinforcement. This probability determines the value of the RR. For example, each response on a RR 10 has a reinforcement probability of 0.10.

By varying the value of the RR schedule, the price, and measuring the number of reinforcers delivered at each price, the demand, a demand curve may be established. The usual technique is to run daily sessions at a given price until the daily demand stabilizes. Then, the price is changed and another series of sessions establishes the demand at the new price. And so on, until the entire demand curve is described. The difficulty is that this method is slow and the effects of other variables on the demand curve as a whole will take months to establish. Two modifications to this method have been described which establish a demand curve within a week or within a single session. Both of these methods were used to establish demand curves in the following experiments.

The "weekly" method was used in this experiment which describes a demand curve with five prices by assigning prices in ascending order to each day of the week (Monday through Friday) . This technique has been shown to describe the same demand curve within a single week which took several weeks to determine by the traditional method (Raslear et al, 1988).

Many challenges, pharmacological, toxicological, and environmental, are best confined to a single session. Plus, studies of reinforcer interactions could be greatly accelerated if a reinforcer's demand curve was established on a daily basis while the second reinforcer's demand curve was established weekly. This would allow the entire demand interaction to be described in one week. A means of establishing daily demand curves was described by Etenger and Staddon (1982). Instead of spending one session each week on each price, the daily technique spent one fifth of each session on each price. Thus, the first fifth of each session presented reinforcements on the smallest RR, then after a brief blackout, the next fifth of the session presented reinforcements on the next larger RR. And so on, until the last fifth of the session presented the largest RR. At the end of any 5 day period the same number of minutes was spent in the presence of each price by either method. Initial RR values were determined for each rat during training.

Single reinforcer demand curves. This experiment established demand curves using the "weekly" and "daily" methods. Demand curves for each positive reinforcer (food, and cocaine) and each negative reinforcer (foot shock, and RF) was established at three reinforcement magnitudes using each of the two methods. On a demand curve, changes in reinforcer size are equivalent to changes in cost. That is, for all reinforcer magnitudes of a given reinforcer the same demand curve was produced so long as cost was presented as the unit price, units of reinforcer per response unit (Bickle et al, 1990).

Subjects

All rats were maintained at approximately 350 grams throughout the course of the experiment. If a rat's weight declined below 315 grams (a 10% decrease) supplementary food was provided at the end of that day. Persistent low weight was addressed by lowering the prices for that rat within the experiment until it maintained at least a 350 gram weight. Weekend feeding were adjusted such that Monday AM weights approximated Friday AM weights.

Apparatus

All experimental sessions were conducted in Coulbourn operant test chambers. The chambers was

equipped with three response levers, cue lights over each lever, a house light, and a 45 milligram pellet dispenser. Food reinforcement was Bioserve 45 milligram food pellets. When shock is required as a stimulus it was applied through the grid floor of the test chamber using a Coulbourn programmable constant-current shocker. Experimental conditions which require RF were run in a RF transparent version of the standard Coulbourn rodent test apparatus. The chamber was configured to approximate as closely a possible the standard Coulbourn chamber. A more complete description of these chambers in the apparatus section of the RF detection experiment.

Training. At the start of the experiment, each rat was trained to lever press until is sustains RR 10 performance without difficulty. On the first Monday after reaching this level of performance the experimental demand schedule was instituted.

Mapping Demand Curves. All demand curves were established under steady state conditions (less than 10% variation in the demand at each price for two weeks running). That is, all experimental variables attained a relatively constant value.

Reinforcement with oral cocaine. The oral cocaine reinforcer is discussed separately in section IV.

Results and Discussion

The classic behavioral effect of RF exposure is "work stoppage". The goal of this experiment was to develop methods of answering the question "Is work stoppage an effect on motivation or capacity to perform?". To this question an experiment must include measures of motivation which are independent of the measures of capacity to perform. The second problem comes from the current methods employed to study motivation. These methodologies require time scales (24 hour-per-day testing and weeks on each condition) which are impossible for the typical toxicologiy or pharmacology study. The answer was to attempt to compress the time scales for the motivational aspects of the study to such an extent that sufficient data is collected within a single session to produce the dependant variable of the motivational study, the demand curve. Figures 2 and 3 show the average demand curves for the weekly and daily groups. The functions of the weekly group appear similar to those reported by Rasaler et. al. (1987) and to those reported by studies using traditional methodologies. The functions of the daily group also appear to follow this same pattern, except for the 3 conditions which provided the most food (e.g. more pellets per reinforcer, or more time per component). Under these conditions so many pellets were earned in the early components that performances in the later higher priced components were supressed. It can be concluded then that the daily groups produced useful demand curves provided that conditions which provide large amounts of food early in the session are avoided. The procedure then reduces the acquisition of a demand function to a single 30 minute session which can be replicated on a daily basis. This procedure is well within the requirements of the behavioral toxicologist and behavioral pharmacologist. Furthermore, the interaction of two motivators may be studied simultaneously assigning each motivator to a different manipulandum (e.g. response lever) and by placing one reinforcer on an weekly procedure and the other on the daily procedure.

This procedure holds promise for the study of RF bio-effects, since the question of "work stoppage" remains to be answered. Even though the daily and weekly procedure worked, attempts to maintain RF avoidance and escape failed at 9.3 GHz and 800 W and and 2.04 GHz and 11 KW. In the case of the 9.3 GHz the power was probably too low to be effective. In the case of the 2.04 GHz the frequency was too low. With the trend towards higher power transmitters at all frequencies, it seems likely that it will eventually be possible to test these assumptions. Certainly, any future study of effects of RF exposure on cognitive performance or aging will need to address the issue "motivation or capacity".

The growing application of RF technology to meet military requirements has increased the potential for exposure of USAF personnel. The potential hazard posed by this expanding technology requires an

ongoing study of RF bioeffects to keep pace with new applications and technologies. Furthermore, exposures to new and future sources are likely to involve RF power levels and exposure parameters (e.g., frequency, pulse width, peak power, etc.) which have yet to be studied. Effects on performance are among the most sensitive indices of biological effects (Elder and Cahill, 1984) and will be a necessary part any research program to characterize RF hazards. In addition, many safety issues require understanding potential performance effects. For example, interference with self-rescue or the performance of mission-critical tasks by RF exposure represents just two performance mediated hazards.

III. ESTABLISHING ORAL COCAINE AS A REINFORCER IN RATS USING HOME-CAGE PREEXPOSURE

Abstract

Although oral cocaine is a less potent reinforcer than intra-venous (IV) cocaine; it has advantages over IV cocaine administration in several paradigms. Unfortunately, the demonstration that oral cocaine can be established as a reinforcer for operant behavior in rats has previously been elusive. In this experiment, rats were forced-exposed to cocaine in their home cage water bottles for five days. They were then provided free access to both oral cocaine and plain water for two months. All subjects continued to consume large doses of cocaine despite the presence of the cocaine-free water. Once animals were consuming a stable daily dose of cocaine, they were trained on an operant task. This task consisted of a liquid cocaine reward being delivered intermittently in response to bar pressing. All subjects performed the operant and consumed the cocaine solution reward. When a cocaine-free control (vehicle) was introduced as the reward, responding declined significantly in three of the four subjects. This demonstrates that oral cocaine can be established as a reinforcer for operant behavior and that home cage preexposure can be useful for developing the operant.

Introduction

In order to study the motivational effects of exposure to radio-frequency fields (RF), it is necessary to compare RF-motivated behavior with that of other reinforcers. The purpose of this experiment was to develop a baseline of oral cocaine self-administration which can readily be adapted to an RF environment.

Cocaine self-administration is typically accomplished by implanting an intra-venous (IV) catheter into an animal and allowing the animal to activate IV infusions of cocaine via a conditioned behavior; however, this method of administration is undesirable, because during RF exposure, the implants and sub-dural catheters can alter the pattern of absorption of the RF energy in the exposed animal producing anomalous "hot spots". These "hot spots" could potentially overshadow any other behavior effect.

In addition, oral cocaine self-administration has other advantages. The catheters required for IV administration require an invasive surgical procedure to install, necessitate daily care to prevent clotting and infection, and typically have a short half-life (approximately one to three months). For the purposes of a long-term study of behavioral management, a more labor-free and efficacious method of cocaine administration is desirable. Thus, in some experimental conditions, oral cocaine self-administration is preferable to IV administration.

Unfortunately, oral (aqueous) cocaine can be difficult to establish as a reinforcer for operant behavior for several reasons. (1) There is a slow onset for the reinforcing effects of oral cocaine. (2) The taste of aqueous cocaine (very bitter to humans) may be aversive to rats. And (3) the local anaesthetic properties of cocaine may limit consumption by affecting oral sensations. The cocaine solution leads to a numbing of sensory endings in the mouth, tongue and throat. As a result, the consumption of oral cocaine solutions is probably self-limiting.

Bell et al. (1993) reported that water-deprived Lewis rats responded under a fixed ratio schedule for a liquid cocaine reward but that there was no preference for the cocaine reward over a drug-free vehicle solution. Other studies, though, have demonstrated reinforcing effects of oral cocaine under certain experimental conditions. Rhesus monkeys and C57BL/6J mice self-administering oral ethanol can be trained to administer oral cocaine when a gradual program of cocaine/ethanol substitution was employed (monkeys: Meisch, George, and Lemaire, 1990; mice: George et al., 1991); however, similar training methodologies failed to establish oral cocaine as a reinforcer in Lewis rats (Bell et al., 1992) Also, place preference have been conditioned with schedule-induced polydipsia in rats (Seidman et al., 1992). Significantly, forced-exposure

to cocaine solutions resulted in preferences for cocaine solutions over water when both were freely available to rats (Meert and Janssen, 1992) and C57BL/6By mice (Sershen, Hashim, and Lajtha, 1994). In addition, forced exposure to cocaine-laced food resulted in a preference for cocaine-laced food over drug-free food when both were freely available (Suzuki et al., 1990).

The current study examined whether oral cocaine can be established as a positive reinforcer for intermittently-reinforced schedule-controlled behavior in rats preexposed to oral cocaine in their home cages.

Method

Subjects

Four drug-naive male Sprague-Dawley rats (Charles River Labs, Portage MI) weighing 225-250 grams at the beginning of the experiment served as subjects. They were housed singly under a 12 hour light/dark cycle. Each animal was given approximately 15 grams of rat chow (Purina Mills Inc, St Louis MO) per day before testing, and water was provided *ad libitum* except as noted in the Experimental Procedure. The subjects' weights were monitored daily in order to determine dose rates for cocaine consumption and were managed so as to maintain the animals at no more than 475 grams. At the end of the experiment, the animals weighed from 375-475 grams.

Apparatus

The modular operant chamber (Coulbourn Instrument, Lehigh Valley PA) is equipped with standard operandi and stimuli and is mounted in a sound-proof cubicle. Chamber dimensions are 29.5 cm wide by 32.5 cm high by 25.0 cm deep. The frame consists of a roof, intelligence panel, walls of aluminum, a Plexiglas door, and standard modular grid shock floor. The intelligence panel consists of 3 adjacent columns (each 28.5 cm high by 7 cm wide) of stimuli and operandi. The right and left columns are made up of a standard manipulanda lever 7 cm from the grid floor and a row of cue lights (red, yellow, and green) 3.5 cm above the lever. The center column consists of a solenoid dispensing trough 7 cm above the floor, a jeweled cue light 4 cm above the trough, a lever 9 cm above the jeweled light, a set of cue lamps 3.5 cm above the lever, and a house light 10.5 cm over the cue lamps. The box was also equipped with a relay clicker to signal bar presses, a full-range audio speaker, and a SONalert to signal reinforcement periods. The experimental sessions were controlled and data was collected by a SKED-11 programming system (Snapper, Kadden, and Inglis, 1982) running on a PDP 11/73 computer (Digital Equipment Corp, Maynard MA) that triggered specified experimental events and recorded responses with a resolution of 10 ms. As such, the data records are amenable to extensive analysis of both molar measures such as response rate, responses per component, etc. and more fine measures such as temporal response allocation.

Cocaine. Cocaine HCl and saccharin HCl were obtained from Sigma Chemical Corp. Drug weights were calculated as the salt. Both drugs were dissolved in distilled water at room temperature.

Procedure

Home cage exposure. Each of the subjects were initially given 5 hours access per day to only a solution of cocaine (500 mg/l) and saccharin (500 mg/l). After five days, the cocaine+saccharin solution continued to be available for 5 hours while water was available at all other times. Over a two month period, the saccharin concentration was decreased gradually to 100 mg/l in the drinking solution. The cocaine+saccharin solution was then made available for one hour per day in an operant chamber with water continuously available in-cage at all other times.

Operant Sessions. All experimental sessions took place Monday though Saturday between 7 am and 3 pm. Each daily session consisted of five 10 minute components separated by 1 minute inter-component intervals. In addition, the delivery of a reinforcer was followed by a 15 sec time-out interval.

Session initiation was indicated by the illumination of the house light and the cue lights above the center lever. Each response on the center lever was signaled by a "click" while the responses on the side levers were neither signaled nor recorded. Each reinforcer triggered the operation of the solenoid for 35 centiseconds (releasing a 0.2 ml volume of fluid) and was signaled by extinguishing the house light, flashing the cue lights over the center lever, illuminating the jeweled light over the trough, and sounding a SONalert tone generator for the duration of the reinforcement period.

Operant Training. Once operant training began, no cocaine solution was available for the subjects in their home cage at any time. The animals were hand-shaped to bar press on a continuous reinforcement schedule with 0.2 ml of a cocaine (500 mg/l) and saccharin (100 mg/l) solution as a reinforcer. The schedule requirement was gradually increased to an RR 14 as reliable testing developed. The RR 14 schedule describes a session in which each response has a 7.1% (1 in 14) chance of being reinforced and in which, on average, every 14th response is rewarded. Cocaine concentrations were gradually increased from 500 mg/l to 800 mg/l over the duration of the training period.

Testing. The animals were tested daily with the cocaine and saccharin solution available as a reward. All subjects were fed in the morning before testing at which time their home cage water bottle was removed. After one month, vehicle (100 mg/l saccharin) solution was randomly introduced as the fluid reward in place of the cocaine solution.

Results

Home cage period. During the initial home cage exposure period, all four subjects consumed large amounts of the cocaine solution despite the presence of free water. In the final five days of in-cage cocaine availability, the four subjects consumed averages of 61.4 ± 0.5, 52.2 ± 3.3, 31.3 ± 3.2, and 36.4 ± 7.3 mg/kg per five hour period respectively (Table 1). The dose rate consumption for the subjects is shown in Figure x.

On average, the four subjects drank 122.9 ± 1.0, 104.4 ± 6.7, 62.6 ± 6.4, and 72.7 ± 14.7 ml of cocaine solution per kilogram of body weight per day, respectively, during their last week on the in-cage exposure period. No data was taken on the consumption of cocaine-free water which was always present for the subjects.

Operant sessions. Responding for the oral cocaine reinforcer was maximal early in the session and usually declined after the third 10 minute session (Figure 2). In all subjects, the decline of responding for the cocaine solution corresponded roughly with the appearance of exaggerated tongue chewing and licking behaviors indicating anaesthetic properties of the solution. In addition, there was typically some late term responding (in the final 5 minute component). The average doses consumed by the rats is displayed in Table 2.

A different pattern of responding was observed when vehicle was substituted for the cocaine solution. There was an initial peak in responding followed by a rapid decline which lasted throughout the session (Figure 3). On the gross level, three of the subjects produced significantly less responses for vehicle than for the cocaine solution (Table 3) (Figure 4).

Discussion

Previously, oral cocaine has not been established as a reinforcer for operant behavior in rats as it has been in C57BL/6J mice (George et al., 1991) and rhesus monkeys (LeMaire et al., 1993). Rat liver microsomes have significantly higher (70-fold) affinity for cocaine than do mice liver microsomes (El-Maghribi et al., 1988). In addition, cocaine in rat liver cells (hepatocytes) can be metabolized to a form that irreversibly binds to protein (Bouis & Boelsterli, 1990). Thus, a significant amount of the cocaine consumed by the subjects never reached its neural sites of action. It has been argued that failures to establish oral cocaine as a reinforcer in rats were due to these species differences (Bell et al., 1993). Although Bell et al. (1993) did not demonstrate oral cocaine's reinforcing properties in their paradigm, they did detect locomotor activating effects of cocaine. The presence of locomotor activation suggests that oral administration of cocaine increased brain cocaine levels by behaviorally relevant amounts.

In our experiment, all subjects performed the operant and obtained doses of cocaine solution which have been shown to create preferences in other paradigms (George et al., 1991; McMillen et al., 1993; Meert & Janssen, 1992). In addition, when a vehicle solution was introduced instead of the cocaine solution, responding on the operant task decreased by significant levels.

Bell et al. (1993) showed in their study that the higher levels of responding for cocaine solution over vehicle were due to general increases in locomotor behavior which were dose-dependently induced by the cocaine. In the current experiment, however, the fact that the subjects delivered more responses for cocaine solution than vehicle solution can not be explained by a "general locomotor activation" phenomenon. Between sessions, the subjects encountered a 2 minute inter-component interval which was lengthened by task-irrelevant responses. These non-specific responses during the time-out had the highest occurrence between the first and second components. If there was general locomotor activation, there should be an INCREASE in non-specific responding during the time-outs as the session progressed. This was not the case. In addition, increases in locomotor activation would be indicated by increases in response rate through the session. Likewise, this was not the case. Response rate was fairly consistent throughout the one hour component. While locomotor analyses were not performed to confirm the lack of general activation, it is highly unlikely that the increased responding for cocaine over vehicle was due to a locomotor effect and not to a reinforcing one.

Another potentially critical feature of our experiment was the maintenance of the operant with the cocaine only. Bell et al. (1993) used water-deprived Lewis rats in their experiments based on previous studies that water-deprivation increases the reinforcing effects of IV-administered cocaine (Carroll and Boe, 1983). In a water-deprived rat, a liquid cocaine solution probably had dual reinforcing properties: the drug-induced euphoric effects and the thirst-satiating effects. Thus, the operant was being maintained by two effects. In our experiment, care was taken to avoid such reinforcer-interactions which could alter behavioral reinforcement by the oral cocaine.

In sum, oral cocaine can be established as a reinforcer for operant behavior in rats. Undoubtedly, the consumption of the orally delivered reinforcer is significantly different than that for a IV-delivered one. Typically, responding for IV-administered cocaine rewards is vigorous and robust. In our paradigm, we find that responding was consistent for an initial period of the session, but thereafter, responding was sporadic or non-existent. This was quite possibly due to the local anesthetic properties of the oral cocaine.

Despite differences between IV and orally-administered cocaine, the oral administration paradigm has numerous uses. As previously stated, oral cocaine is advantageous when the experimental procedure calls for a self-administering animal who is surgically unaltered (e.g. an experiment requires that the animal placed in an RF environment). In addition, the orally self-administering animal is much more desirable for long-term behavioral experiments that might otherwise be limited by the short life span of functional IV catheters.

IV. TEMPERATURE SENSITIVE PAINT REVEALS CHANGES IN SURFACE TEMPERATURE DURING 9.3 and 2.4 GHz EXPOSURE.

Introduction

Paints which change color at known temperatures were used to measure the surface temperature of shaved rat cadavers during exposure to pulsed 9.3 GHz or 2.4 GHz radio-frequency (RF) fields. Exposures to 9.3 GHz (0.23 W/cm^2) in HKE-orientation produced rapid color change in both ears. Exposures to 2.4 GHz (1.0 W/cm^2) in KHE-orientation revealed a hot spot on the forehead.

Surface heating during RF exposure is a behavioral stimulus. We used temperature sensitive paint as a measure of the distribution of RF energy and surface heating in RF exposed rat cadavers. Others have used painted cloth soaked with water to visualize RF fields (Sherry, Walters, & Brewer, 1994; personal communication).

Method

The paint (Matsui International Co. Ltd., Japan., Type 27) changes color at 33 °C. Three components (pigment, binder and fixer) are mixed, applied to a shaved rat cadaver, allowed to dry, and cured at 100°C for 3 minutes. After returning to room temperature (22 °C), the rat was exposed to the RF field. Pigment-only applications avoided curing, shortened total drying time to less than 10 minutes, and had the same thermal-sensitive properties of the cured paint. All exposures were video taped.

Results and Discussion

Comparison of normal video images with infrared video images and data collected by others (Walters et al., 1995) with implanted temperature probes verified the utility of the paint and pigment-only preparations. Contour plots were constructed from digitized video images. Rates of temperature change were calculated from exposure duration at time of color change and difference between starting and color change temperatures. A contour plot resulting from a 2.4 GHz HKE-orientation exposure is shown in the lower panel of Figure 4.

Changes in surface temperature contribute to RF behavioral effects by stimulating thermal receptors. Visualizing these temperature changes required expensive infrared cameras. Heat sensitive paint provides an easy alternative. The cured paint is permanent and reusable. For single-use samples, the uncured pigment was preferable. Results may be used qualitatively to visualize the RF field or quantitatively.

V. REFERENCES

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Figure Captions

Figure 1. Probabilities of hits (filled squares) and false alarms (filled circles) as a function of specific adsorbtion rate (SAR). Error bars indicate mean plus and minus one standard error of the mean. So long as the probability of hits is greater than the probability of errors the RF signal is being detected at above chance levels. The data for Rat 121, 124, 126 show reliable detection at less then 1 mW/g SAR. Rat 125 is failing to detect a much higher level of RF. This rat never learned the discrimination to the extent of the previous 3 possibly due to this rats habit of placing its head in the food cup whenever possible. Rat 122 (top right) show good detection albeit at a higher SAR (2-4 mW/g).

Figure 2. Mean response rates plus and minus a standard error of the mean for all rats in the "Weekly" group as a function of the number of responses required per pellet. Each curve represents one combination of the number of pellets per reinforcer and component duration. Curves with the same symbol have the same unit price. For example, the unit price for a pellet of food is the same in the 2nd condition where 1 pellet per reinforcement and 600 sec components have the same price as the third condition where 2 pellets of food are delivered per reinforcement and components are only 300 sec long.

Figure 3. Mean response rates plus and minus a standard error of the mean for all rats in the "Daily" condition. Each curve represents the mean of the last ten day of all replications of each combination of the number of pellets per reinforcer and component duration. Curves with the same symbol have the same unit price. For example, the unite price for a pellet of food is the same in the forth conditions 2 pellets and a 600 sec compenent duration as the fifth condition which haas 4 pellets per reinforcer but only a 300 second component duration. The three curves which produced the lowest response rates represent the conditions which had the lowest unit price for food. While the remaining conditions produced higher response rates similar to those seen in the "Weekly" group in Figure 2.

Figure 4. The top panel shows a photograph of the rat as it was positioned during exposure. The bottom panel shows a grey scale, contour plot of the time each area of the rat required to reach the temperature required to cause the paint to change color. The ears, fore paws and testicles changed especially rapidly.

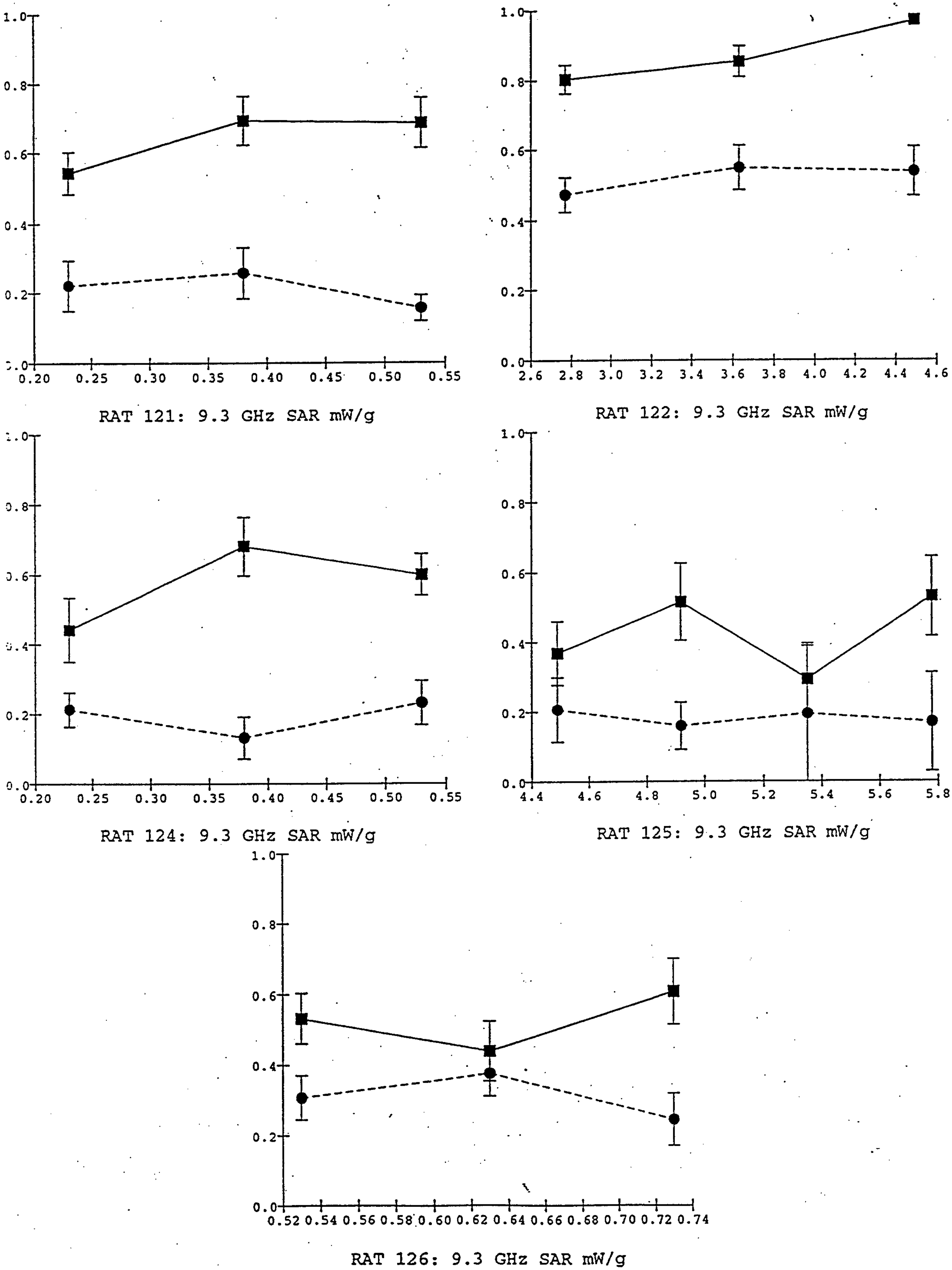

Figure 1. Probabilities of hits and false alarms versus specific absorption rate.

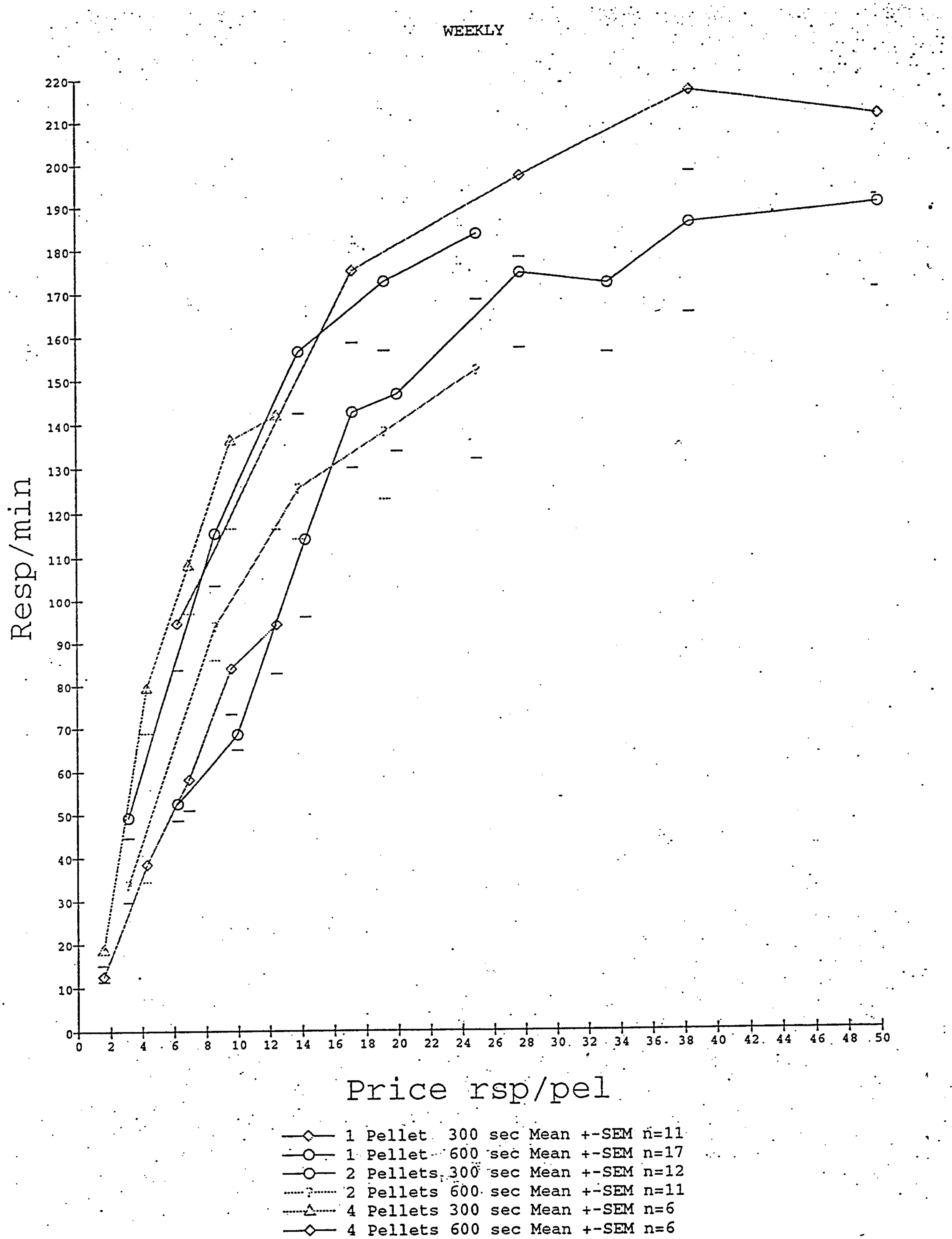

Figure 2. Mean response rates as a function of number of responses per pellet.

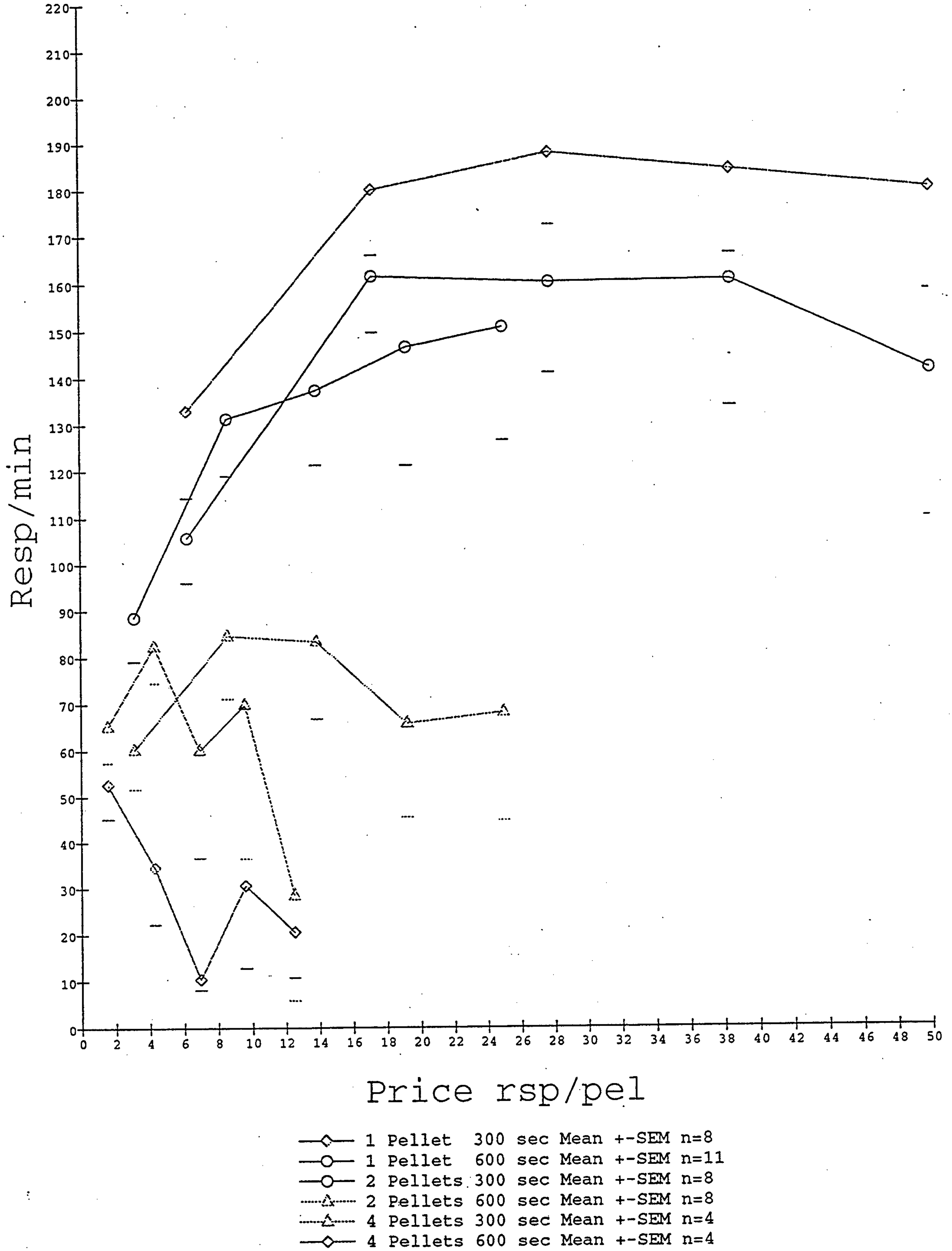

Figure 3. Mean response rates for all rats.

Figure 4. Photograph of rat as positioned during exposure.